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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/824,322	04/02/2001	Brenda F. Baker	ISPH-0501	9406

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EXAMINER
SCHULTZ, JAMES

ART UNIT	PAPER NUMBER
1635	13

DATE MAILED: 05/07/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/824,322	Applicant(s) BAKER ET AL.	
	Examiner James D. Schultz	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). 11 .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 1 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim13 of U.S. Patent No. 6,228,642. Although the conflicting claims are not identical, they are not patentably distinct from each other because both claims are drawn to a method of antisense-mediated inhibition of tumor necrosis factor-α (TNF-α) *in vivo*. Claim 13 of U.S. Patent No. 6,228,642, drawn to a method of antisense-mediated inhibition of TNF-α in adipose tissue, anticipates the broader claim 1 of the instant application, which is drawn to a method of antisense-mediated inhibition of TNF-α in any tissue *in vivo*, Thereby embracing the claimed invention of claim 13.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, and 3-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of colitis and rheumatoid arthritis using antisense compound ISIS 25302, does not reasonably provide enablement for methods of using the full spectrum of antisense sequences complementary against any portion of TNF-α to inhibit its expression as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The specification as filed does not provide sufficient guidance that would enable a skilled artisan to successfully employ methods of using said compounds, other than Isis 25302, in *in vivo* environments. Although the specification prophetically considers and discloses general methodologies of using other claimed constructs *in vivo* or in methods of inhibition or treatment, such a disclosure would not be considered enabling since the *a priori* prediction of target inhibition by antisense molecules based on sequence complementarity alone is highly unpredictable. As illustrated below, in the absence of guidance regarding which antisense sequences are inhibitory against said target *in vivo*, undue experimentation would be required from one of ordinary skill in the art to have had practiced the invention as claimed.

Such unpredictability is due to obstacles that still face oligo therapy, as quoted here by Agrawas, who states the following: "(t)here are two crucial parameters in drug design: the first is the identification of an appropriate target in the disease process, and the second is finding an appropriate molecule that has specific recognition and affinity for the target, thereby interfering in the disease process" (Page 376); [c]ellular uptake of oligonucleotides is complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum. [i]t is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency." (Page 378); "[a]ny antisense activity observed in such artificial systems [cell culture] should be scrutinized carefully with respect to the disease process and its applicability to *in vivo* situations." (Page 379). Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target genes. (Pages 34-36).

Branch further elucidates the unpredictability of *in vivo* oligo therapy by stating that "the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curves and therapeutic index is available" (Page 46, second column) and, "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules" (Page 45, third column). Additionally, in a recently published review of the potential use of antisense oligos as therapeutic agents, Gewirtz et al. teach that the inhibitory activity of an oligo depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target. (Page 3161, second and third columns). Gewirtz et al.

observes that the "antisense approach has generated controversy with regard to mechanisms of action, reliability, and ultimate therapeutic utility" and "that efforts should be increased... to learn how they may be used successfully in the clinic (Page 3162, middle column, last paragraph). Branch concludes that "non-antisense effects are not currently predictable, and rules for rational design cannot be applied to the production of non-antisense drugs. These effects must be explored on a case by case basis" (Page 50). Although applicant has demonstrated that ISIS 25302 works *in vivo* against TNF-a-mediated rheumatoid arthritis and colonitis, the specification of the instant application fails to give guidance as to how to overcome the unpredictability and challenges in the oligo therapy art that are exemplified in the references above, and thus does not provide adequate guidance for one of skill in the art to practice the invention as claimed.

Further, one skilled in the art would not accept on its face the examples given in the specification of the method of inhibiting TNF-a-mediated rheumatoid arthritis and colonitis using ISIS 25302 as being correlative or representative of successful methods using antisense compounds other than ISIS 25302 to inhibit TNF-a inflammatory diseases. This is particularly true in view of the lack of guidance in the specification regarding the efficacy of non- ISIS 25302 compounds and known unpredictability associated with methods of using antisense compounds to inhibit target genes *in vivo*. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with appropriate *in vivo* accessibility, delivery, and treatment effects mediated by antisense administration, and specifically regarding the instant methods claimed.

Said claims are drawn to methods of treating an inflammatory disorder in an individual, comprising the administration of any antisense oligonucleotide which is complementary to the nucleotide sequence of TFN-a. While applicant has enabled ISIS 25302 in treating colonitis and rheumatoid arthritis *in vivo*, the quantity of experimentation required to practice the invention as claimed using all other complements to said target *in vivo* would require the *de novo* determination of accessible target sites, modes of delivery, and importantly, formulations to target appropriate cells and /or tissues harboring the target mRNA such that all TNF-a expression is inhibited appropriately *in vivo*. Since the specification fails to provide any guidance for the successful use of a method to inhibit TNF-a-mediated inflammatory diseases using non-ISIS 25302 antisense molecules, and since the specification provides no guidance for resolving factors related to unpredictability in targeting said gene in an individual, one of ordinary skill in the art would be unable to practice the invention as presented in the specification over the scope claimed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

J. Douglas Schultz, Ph.D.

May 3, 2002

ANDREW WANG
PRIMARY EXAMINER